REMARKS

Claims 1, 2, 18, 19, 23 to 40, and 46 to 47 are pending. Applicants propose to cancel claims 3-5, 20-22, and 41 to 45. Applicants also propose to cancel claims 37 to 40 as allegedly drawn to a separate invention. Applicants propose to add new claims 48 to 59. Support for new claim 48 is found at page 13, line 25, to page 14, line 7. Support for new claims 49 to 59 is found, e.g., at page 11, line 30, to page 12, line 14. These amendments would add no new matter.

In addition, the amendment set forth herein would raise no new issues that would require further consideration and/or search. Applicants submit that this amendment would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. 1.116 (a).

Applicants thank the Examiner and his supervisor for the telephone interview on October 15, 2001, and the follow-up interviews on February 1 and 13, 2002 . In the following remarks, applicants will address both the issues raised in the Office Action dated June 15, 2001, and discussed during the telephone interviews.

35 U.S.C. § 112, First Paragraph

Claims 1-6, 18-36, and 41 to 47 have been rejected for an alleged lack of written description. Of these, claims 1, 2, 18, 19, 23 to 36, 46, and 47 are pending. The Office Action rejects the claims stating that they "are directed to methods of identifying compounds" "that have not been disclosed in the specification" (Office Action at page 3). The Office Action further states that applicants were not in "possession of the claimed genus of compounds" (*id.*). As discussed during the telephone interview of October 15, 2001, applicants submit that the claims at issue are method claims, and not claims to compounds.

The Office Action characterizes the pending claims as "directed to methods of identifying compounds corresponding to peptides, peptidomimetics, a small organic molecule or a small inorganic molecules [sic]" (Office Action at page 3). The Office Action also discusses

"compounds encompassed by the claims," "[t]he claimed genus of compounds," and "the genus of the compounds claimed" (Office Action at page 3). Applicants respectfully assert that these are not accurate characterizations of the claims. Applicants are claiming a method for identifying compounds. Applicants are not claiming any compounds *per se*.

During the telephone interview conducted on October 15, 2001, the Examiner indicated that he found the above arguments persuasive and would withdraw the rejection. In view of the above remarks and the telephone interview, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

35 U.S.C. § 102 (e)

Claims 1, 2, 18, 19, and 23 to 26 have been rejected as allegedly anticipated by McKay et al. (U.S. Patent No. 5,877,309). The Office Action maintains that the term "small organic molecules" covers oligonucleotides; a class of compounds disclosed in McKay.

In view of the telephone interview on February 13, 2002, applicants understand that the Examiner has agreed to withdraw this rejection. In the interview, applicants explained their position that the Office Action has misinterpreted "small organic molecules" as including oligonucleotides. According to the specification, compounds that may be used in connection with the claimed methods include "peptides and other organic compounds (*e.g.*, peptidomimetics) that bind to a JNK3 protein and inhibit its activity in any way" (specification at page 13, lines 3-6). The specification also lists the types of peptides, libraries of known compounds, and the use of computer and molecular modeling systems to design compounds that can be used in accordance with the claimed methods (specification at pages 13-15). The specification then refers to non-peptide molecules in its further discussion of "small organic or inorganic molecules" (see the specification at page 13, lines 16). Finally, in a completely separate section of the specification, antisense constructs and oligonucleotide based therapies are discussed (see the specification at page 22, line 3, to page 30, line 4).

Furthermore, applicants' deliberate distinction of the terms is in accordance with the meaning and standard usage of the terms by those skilled in the art. Thus, given the applicants' distinction of the terms "small organic molecules" and "oligonucleotides" and the distinction of

these terms as understood by those skilled in the art, it was clearly applicants' intention not to encompass oligonucleotides by the term "small organic molecules."

Applicants point out that claim 23 does not even contain the term "small organic molecule." Thus, the rejection as discussed in the Office Action does not seem to apply to this claim. Nor does this aspect of the rejection apply to claims 24 to 26 which depend from claim 23 and do not contain the term. In addition, claim 23 includes a step of administering a selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity. Nowhere does McKay discuss excitotoxicity. Therefore, McKay cannot anticipate the invention of claim 23 or those claims that depend from claim 23.

Thus, as the claimed methods do not encompass the use of oligonucleotides to identify inhibitors of JNK3 expression, McKay cannot anticipate the claims. In view of the above, and the telephone interviews, applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

35 U.S.C. § 103 (a)

Claims 3, 4, 20, 27 to 31, and 41 to 47 have been rejected as allegedly obvious over several references. Of these, claims 27 to 31, 46, and 47 would be pending after entry of the proposed amendment. The Office Action characterizes all of these claims as being drawn to

> a method of identifying compounds that modulate the activity (phosphorylation of a substrate such as c-Jun) of JNK3 wherein the method comprises incubating the cell that has JNK3 activity with a compound under conditions and time sufficient for the cell to express JNK3 activity, wherein the compound is a peptidomimetic, a small organic molecule or a small inorganic molecule... (Office Action at page 5)

Applicants do not agree with the characterization. Pending claim 31 states that the compound is a peptide (omitted from the description in the Office Action), peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide (omitted from the description in the Office Action). These compounds are not recited in claims 27 to 30, 46, or 47. Applicants also note that claims 27 to 31 are drawn to a method of identifying JNK3 activity. Claims 46 and 47

are drawn to methods of identifying a compound that inhibits JNK3 phosphorylation of a substrate. Claims 27 to 31, 46, and 47 include a step of administering a selected compound to an animal model of an excitotoxic disorder, and assaying the animal for excitotoxicity.

In addition, new claims 48 to 59 are drawn to methods for identifying a candidate compound for treatment of a neuronal disorder or a disorder related to excitotoxicity.

Rejections over Gomez del Arco, Lander, Gupta, and Nadler

Claims 3 to 4, 20, 27 to 31, and 41 to 47 have been rejected as allegedly obvious in view of a combination of four references: Gómez del Arco (referred to as "Arco" in the Office Action), Lander, Gupta, and Nadler. Of these, claims 27 to 31, 46, and 47 would be pending after the proposed amendment. Applicants respectfully disagree with the rejection.

Applicants assert that the references cited by the Examiner do not establish a *prima facie* case of obviousness because the Examiner has failed to satisfy the prerequisite for combining references:

> Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103, the teachings of references can be combined only if there is some suggestion or incentive to do so. ACS Hosp. Sys., Inc. v. Montefiore Hosp. 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984) (emphasis in original).

First, Gómez del Arco is cited for showing that antioxidant agents activate JNK in Jurkat cells. The Office Action acknowledges that Gómez del Arco does not teach JNK isoforms or excitotoxicity. Applicants point out that not only does the reference not teach JNK isoforms, but there is also no evidence that Gómez del Arco detected JNK3 activity. Indeed, since Gómez del Arco used Jurkat cells which are derived from a T-cell leukemia line and JNK3 is expressed primarily in nervous tissue and testis, there is no reason to expect that Gómez del Arco could have detected JNK3 activity. Thus, there is no evidence that JNK3 was detected, nor that one skilled in the art would have known that the molecules used in Gómez del Arco would activate JNK3.

Lander involves the finding that NO_x can activate JNK in Jurkat cells. The Office Action admits that "[Lander] does not teach the different isoforms of the JNK nor does it teach the excitatory experiment involving an animal model" (Office Action at page 7). Applicants agree with this and add that there is no evidence that Lander detected JNK3 activity, particularly since Jurkat cells were used in the reported experiments. There would be no expectation that this finding would apply to JNK3.

Nadler shows that intraventricular kainic acid destroys CA3 hippocampal neurons. The reference teaches nothing whatsoever about any JNK, much less JNK3 activity or phosphorylation of a JNK3 substrate.

Gupta discloses JNK3 and the activation by IL1 of JNK3 transfected into Chinese hamster ovary cells. Nothing in Gupta suggests that JNK3 is associated with excitotoxicity, much less an assay for modulators that included an assay for excitotoxicity.

There is no suggestion in any of these references to combine them to provide applicants' claimed methods of identifying compounds that modulate JNK3 expression, activity, or binding. Only Gupta even discusses JNK3, and the only reference discussing excitotoxicity (Nadler) has nothing to do with JNK, much less JNK3. Furthermore, the Office Action does not point to any motivation to combine these references except for conclusory statements based on the assumption that if one has tested one isoform of JNK, then all other isoforms are expected to behave in the same way. For example, the Office Action states "[a]s Gupta et al. show that they have isolated 10 isoforms of JNK from human brain, one of ordinary skill in the art would be motivated to identify compounds that modulate the activity of the JNK3 in the brain by performing the excitotoxic assay using kainic acid as taught by Nadler et al." (Office Action at page 8), but there is no factual or evidentiary support for this conclusion.

Applicants respectfully submit that this lack of support vitiates the alleged obviousness rejection. The Office Action fails to provide any reason for specifically choosing JNK3 from the many isoforms that Gupta describes, or for linking any JNK, much less JNK3, to excitoxicity. As discussed above, it is questionable whether any of the other references even disclose JNK3. Certainly none of them provide any suggestion that would link JNK3 to

excitotoxicity and certainly nothing is discussed in the art that would suggest the combination that is disclosed in the claimed invention.

In view of the above discussion, applicants respectfully request that the rejection of claims 27 to 31, 45, and 46 over Gómez del Arco, Lander, Gupta, and Nadler be withdrawn.

Rejection over Gupta and Nadler

Claims 5, 21, 22, and 32 to 36 have been rejected for alleged obviousness in view of Gupta and Nadler. Of these, claims 32 to 36 would be pending after the proposed amendment. Again, the Office Action fails to present any evidence that one in the art would have been motivated to combine these references. As discussed above, Nadler discloses nothing whatsoever about JNK, much less JNK3. Nor does anything in Gupta suggest that JNK3 has anything to do with excitotoxicity, nor does it suggest an assay for compounds that modulate JNK binding. Nor does the Office Action provide a reason why one in the art would have selected JNK3 out of the many JNK isoforms identified in Gupta. The Office Action does not point to any suggestion to combine these references, but merely asserts that "one of ordinary skill in the art would be motivated to identify compounds that modulate the binding of JNK3 in the brain by performing the excitotoxic assay...taught by Nadler et al." (Office Action at page 10) to make the present invention. The Office Action also states "one of ordinary skill in the art would have a reasonable expectation of success since Gupta et al. teach the existence of several isoforms of JNK as well as a binding assay and Nadler et al. provide a time tested method of inducing excitotoxic disorder in an animal using kainic acid" (Office Action at page 10). These assertions are mere general conclusions without specific factual support and thus are not sufficient to establish a prima facie case for obviousness. There is no teaching, suggestion, or motivation to combine the cited references and the rejection is therefore improper.

Applicants assert that without their disclosure, there would have been no motivation at the time of the invention to combine Nadler and Gupta, even if these references suggested all of the elements of the invention.

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success,

> viewed in the light of the prior art. . . . (citations omitted). Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

In view of the above cited test, and the lack of any showing to suggest the proposed combination of Gupta and Nadler without reading applicants' disclosure, applicants submit that the rejection of claims 32 to 36 over Gupta and Nadler is unsupported and should be withdrawn, which action is respectfully requested.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be examined. This Amendment is being filed with a request for continued patent application. All fees believed to be owed are enclosed with the application. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10363-005002.

Respectfully submitted,

Date: April 5, 2002

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In the claims:

Claims 3 to 6, 20 to 22, and 41 to 45 have been cancelled.

Claims 48 to 49 have been added.

FOR CONVENIENCE, ALL OF THE PENDING CLAIMS ARE LISTED BELOW.

1. (Amended) A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell; and

comparing the amount of JNK3 expression in the presence and absence of the compound, wherein a difference in the level of expression indicates that the compound modulates JNK3 expression.

2. The method of claim 1, wherein the compound decreases the expression of JNK3.

18. The method of claim 1, wherein the compound is a soluble peptide.

19. The method of claim 1, wherein the compound is a phosphopeptide.

23. A method of identifying a compound that modulates JNK3 expression, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions and for a time sufficient for the cell to express a JNK3 protein absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 expression in the cell in the presence of the compound;

measuring JNK3 expression in the control cell;

comparing the amount of JNK3 expression in the presence and absence of the compound;

selecting the compound if there is a difference in the level of expression in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the compound modulates JNK3 expression.

24. The method of claim 23, wherein the compound decreases the expression of JNK3.

25. The method of claim 23, wherein the animal model is a mouse model.

26. The method of claim 23, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

27. A method of identifying a compound that modulates JNK3 activity, the method comprising:

incubating a cell that exhibits JNK3 activity with a compound under conditions and for a time sufficient for the cell to exhibit JNK3 activity absent the compound;

incubating a control cell under the same conditions and for the same time absent the compound;

measuring JNK3 activity in the cell in the presence of the compound;

measuring JNK3 activity in the control cell;

comparing the amount of JNK3 activity in the presence and absence of the compound;

selecting the compound if there is a difference in the level of activity in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity, wherein a decrease in excitoxicity in the animal indicates that the compound modulates JNK3 activity.

28. The method of claim 27, wherein the animal model is a mouse model.

29. The method of claim 27, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

30. The method of claim 27, wherein the compound decreases JNK3 activity.

31. The method of claim 27, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

32. A method of identifying a compound that modulates the binding of a JNK3 polypeptide to a substrate, the method comprising:

comparing the amount of a JNK3 polypeptide bound to a substrate in the presence and absence of a compound;

selecting the compound if there is a difference in the amount of JNK3 polypeptide bound to the substrate in the presence and absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the selected compound modulates the binding of a JNK3 polypeptide to the substrate.

33. The method of claim 32, wherein the animal model is a mouse model.

34. The method of claim 32, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

35. The method of claim 32, wherein the binding of a JNK3 polypeptide to a substrate is decreased.

36. The method of claim 32, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

37. A method of identifying a compound that modulates JNK3- mediated excitotoxicity, the method comprising

administering a test compound to an animal model of an excitotoxic disorder; and

assaying the animal for excitotoxic effects, wherein a decrease in excitotoxic effects in the presence of the test compound compared to an untreated control indicates that the compound modulates JNK3 excitotoxicity.

Has been cancelled.

38. The method of claim 37, wherein the animal model is a mouse model.

39. The method of claim 37, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

40. The method of claim 37, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, a small inorganic molecule, or an oligonucleotide.

46. A method of identifying a compound that inhibits phosphorylation of a JNK3 substrate, the method comprising:

comparing the amount of a JNK3 substrate phosphorylated in the presence and absence of a compound;

selecting the compound if there is a decrease in the amount of JNK3 substrate phosphorylation in the presence compared to the absence of the compound; and

administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity,

wherein a decrease in excitotoxicity in the animal indicates that the selected compound inhibits the phosphorylation of a JNK3 substrate.

47. The method of claim 46, wherein the JNK3 substrate is c-Jun.

48. (New) The method of claim 23, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule.

49. A method of identifying a candidate compound for the treatment of a disorder related to excitotoxicity, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions sufficient to express the JNK3 protein;

incubating a control cell under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a disorder related to excitotoxicity.

50. A method of identifying a candidate compound for the treatment of a disorder related to excitotoxicity, the method comprising:

incubating a JNK3 protein with a JNK3 substrate and a compound under conditions sufficient to allow the interaction of the JNK3 protein with a JNK3 substrate;

incubating a the JNK3 protein and the JNK3 substrate under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a disorder related to excitotoxicity.

51. A method of identifying a candidate compound for the treatment of a neuronal disorder, the method comprising:

incubating a JNK3 protein with a JNK3 substrate and a compound under conditions sufficient to allow the interaction of the JNK3 protein with the JNK3 substrate;

incubating the JNK3 protein and the JNK3 substrate under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a neuronal disorder.

52. A method of identifying a candidate compound for the treatment of a neuronal disorder, the method comprising:

incubating a cell that can express a JNK3 protein with a compound under conditions sufficient to express the JNK3 protein;

incubating a control cell under the same conditions and for same time absent the compound; and

comparing the level of JNK3 activity in the presence and absence of the compound, wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound for the treatment of a neuronal disorder.

53. The method of claim 49, 50, 51, or 52, wherein the compound is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule.

54. The method of claim 49, 50, 51, or 52, wherein the compound inhibits the ability of JNK3 to phosphorylate a substrate.

55. The method of claim 54, wherein the substrate is c-Jun.

56. The method of claim 49, 50, 51, or 52, wherein the compound inhibits the ability of JNK3 to bind a substrate.

57. The method of claim 56, wherein the substrate is c-Jun.

58. The method of claim 49 or 50, wherein the excitotoxic disorder is kainic acid-induced or pentetrazole-induced.

59. The method of claim 49, 50, 51, or 52, wherein the disorder is a seizure disorder, epilepsy, cerebrovascular disorder, ischemia, spinal cord injury, spinal cord pressure, dementia, Alzheimer's disease, Parkinson's disease, a neurogenerative disorder, Huntington disease, or motoneuron disease.--